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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,040	07/18/2006	Isabelle Meynial-Salles	2912956-029000	8536

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Baker Donelson Bearman, Caldwell & Berkowitz, PC
920 Massachusetts Ave, NW
Suite 900
Washington, DC 20001

EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
09/16/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroomdc@bakerdonelson.com
ltapp@bakerdonelson.com
rseward@bakerdonelson.com

Office Action Summary	Application No.	Applicant(s)	
	10/585,040	MEYNIAL-SALLES ET AL.	
	Examiner	Art Unit	
	YONG PAK	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2010*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-6,9-14,16,17,22-27,30-36 and 39-50* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-6,9-14,16,17,22-27,30-36 and 39-50* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/FR05/00070.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 27, 2010 has been entered.

Claims 1-6, 9-14, 16-17, 22-27, 30-36, and 39-50 are pending and are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on August 27, 2010, have been fully considered and are deemed to be persuasive to overcome some of the objections/rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

In view of the amendment of claims 16 and 34, the objections to claims 16 and 34 have been **withdrawn.**

Claims 10-11 and 40-41 are objected to because the claim recites "*ctfA and B*" instead of "*ctfAB* ".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 9-14, 16-17, 22-27, 30-36, and 39-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-6, 9-14, 16-17, 22-27, 30-36, and 39-50 are drawn to **(A)** a strain of evolved microorganism, bacterium, *Escherichia* or *Corynebacterium* comprising a deletion of the tpiA gene and deletion of at least one gene involved in conversion of methylglyoxal into lactate or deletion of *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd*, wherein said strain having an improved synthesis of 1,2-propanediol, and **(B)** a method of preparing said strain of (A). Therefore, these claims encompass a strain of any or all microorganism, bacterium, yeast, fungus, *Escherichia* and *Corynebacterium* comprising **(A)** a deletion of the tpiA gene and deletion of any or all genes involved in conversion of methylglyoxal into lactate or deletion of *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd*, wherein said strain having an improved synthesis of 1,2-propanediol and **(B)** a method of preparing said strain of (A). Therefore, these claims are drawn to a genus of any or all microorganism, bacterium, *Escherichia* and *Corynebacterium*

comprising a deletion of the tpiA and any gene involved in conversion of methylglyoxal into lactate, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE, and/or edd*, wherein said strain has an improved synthesis of 1,2-propanediol. The specification describes an *E. coli* comprising deletions of its endogenous *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd*, wherein said *E. coli* has improved 1,2-propanediol synthesis. However, the specification does not provide an actual reduction to practice of the claimed microorganism because the specification fails to disclose the structure of *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd*, genes in non-*E. coli,* which must be known in order to inactivate said genes in the claimed microorganism. The specification does not disclose the isolation or cloning of any non-*E. coli tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd*, genes. The specification does not describe any structural features of non-*E. coli tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd*, genes that would have been expected to be shared by other any or all microorganism, bacterium, *Escherichia* and *Corynebacterium tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes. The level of knowledge and skill in the art does not allow those skilled in the art to structurally envisage or recognize any or all microorganism, bacterium, *Escherichia* and *Corynebacterium tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes because it is known that corresponding genes in different species tend to differ in sequence and the amount and type of sequence variation is unpredictable. Since the structure of the *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes would be expected to vary unpredictable from the structure of *E. coli tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes, the disclosed *E. coli*

strain comprising deletion of its *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* do not constitute a representative number of species to describe the whole genus of any or all microorganism, bacterium, *Escherichia* and *Corynebacterium* comprising deletion of *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes and there is no evidence on the record of the relationship between the structure of the disclosed *E. coli* strain and the structure of any or all microorganism, bacterium, *Escherichia* and *Corynebacterium* comprising deletion of *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes. Because the *E. coli* strain comprising deletion of its *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes is not representative of the entire claimed genus, and the specification does not disclose structural features shared by members of the genus, the description of the modified *E. coli* comprising deletion of its *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes would not have put the application in possession of the common structural attributes or features shared by members of the genus that structurally distinguish the members of the genus from other materials at the time of filing. Thus, the description of the *E. coli* comprising deletion of its *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes is not sufficient to describe the claimed genus of any or all microorganism, bacterium, *Escherichia* and *Corynebacterium* comprising deletion of its *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes. Accordingly, the specification does not provide a representative number of species or sufficient common structural features to show that the application would have been in possession of the claimed genus as a whole at the time of fling. Therefore, the specification fails to describe a representative species of the genus

comprising any or all yeast or genus comprising any or all microorganism, bacterium, *Escherichia* and *Corynebacterium* comprising comprising deletion of its *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 1-6, 9-14, 16-17, 22-27, 30-36, and 39-50.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants argue that the claims meet the written description requirement because the specification provides a framework by which to perform the claimed methodology on non-*E. coli* genes and in conjunction with databases available, one of ordinary skill in the art would be able to identify the structure of a wide range of corresponding genes in organisms outside of *E. coli*.

Examiner respectfully disagrees. The instant rejection is not an enablement rejection examining whether one having ordinary skill in the art would have been able to make/practice the claimed invention, but rather if the claimed subject matter is

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a wide genus comprising of any or all microorganism, bacterium, *Escherichia* and *Corynebacterium* comprising a deletion of its endogenous tpiA and any gene involved in conversion of methylglyoxal into lactate, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE, and/or edd*, wherein said strain has an improved synthesis of 1,2-propanediol. The specification does not describe any structural features of non-*E. coli tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd*, genes that would have been expected to be shared by all the members of the claimed genus. The level of knowledge and skill in the art does not allow those skilled in the art to structurally envisage or recognize any or all microorganism, bacterium, *Escherichia* and *Corynebacterium tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes because it is known that corresponding genes in different species tend to differ in sequence and the amount and type of sequence variation is unpredictable. The specification does not provide an actual reduction to practice of the claimed microorganism because the specification fails to disclose the structure of *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd*, genes in non-*E. coli,* which must be known in order to inactivate said genes in the claimed microorganism. Because the *E. coli* strain comprising deletion of its *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,* and/or *edd* genes is not representative of the entire claimed genus, and the specification does not disclose structural features shared by members of the genus, the description of the modified *E. coli* comprising deletion of its *tpiA*, *gloA, aldA, aldB, ldhA, pflA, pflB, adhE,*

and/or *edd* genes would not have put the application in possession of the common structural attributes or features shared by members of the genus that structurally distinguish the members of the genus from other materials at the time of filing.

Hence the rejection is **maintained**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 5-6, 9-14, 16, 22-24, 26-27, 30-32, 35-36, 39-46, and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cameron et al., Altaras et al. and Bermejo et al.

Claims 1-2, 5-6, 9-14, 16, 22-24, 26-27, 30-32, 35-36, 39-46, and 48-51 drawn to an *E. coli* comprising a deletion of its *tpiA*, *gloA,* and *ldhA* genes and expression of heterologous *adc*, *ctfAB* and *thl* genes from *C. acetobutylicum* and comprising evolved genes encoding enzymes that increases synthesis of 1,2-propanediol and a method of producing said *E. coli*.

Cameron et al. (US Patent No. 6,303,352 B1 – cited previously on form PTO-892) discloses a method of modifying *E. coli* to increase production of 1,2-propanediol by deleting its *tpiA* and/or *gloA* genes and over-expressing genes encoding enzymes that increases metabolism of pyruvate to acetate and/or pyruvate to acetyl-CoA and NADH, wherein said *E. coli* has improved 1,2-propanediol synthesis, and a method of producing said *E. coli* (Column 4, line 66 through Column 12, line 16). *E. coli* has an endogenous pyruvate dehydrogenase complex.

The difference between the reference of Cameron et al. and the instant invention is that the reference of Cameron et al. does not teach further “evolution” of the above *E. coli* by evolving genes involved in the biosynthesis pathway from DHAP to methylglyoxal and then to 1,2-propanediol, such as deletion of *ldhaA* and expression of *C. acetobutylicum* gene encoding an enzyme that increases production of acetone.

Altaras et al. (Biotechnol. Prog. 16:940-946 - form PTO-1449) discloses enhanced production of 1,2-propanediol by genetic engineering, comprising deletion of

the *ldhaA* gene in *E. coli* (abstract and page 940). Altaras et al. teaches that elimination of the byproduct, lactate, increases production of 1,2-propanediol (abstract and page 940).

Bermejo et al. (Appl Environ Microbiol. 1998 Mar;64(3):1079-85 - form PTO-892) discloses expression of *C. acetobutylicum adc*, *ctfAB* and *thl* genes encoding an enzyme that increases production of acetone in *E. coli* in order to improve solvent production and an acetone producing *E. coli* may be useful hosts, which decreases the accumulation of detrimental acetate (page 936).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify or evolve the recombinant *E. coli* of Cameron et al. by deleting it's *ldhA* genes and over-express a *C. acetobutylicum* gene encoding an enzyme that decreases accumulation of acetate or gldA and/or mgs. One of ordinary skill in the art at the time the invention was made would have been motivated to do the above for the purpose of eliminating production of the byproduct, lactate, and in order to increase production of 1,2-propanediol and decrease accumulation of acetate. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for success sine Cameron et al. teaches deletion of the *tpiA* and *gloA* gene in E. coli to increase 1,2-propanediol production, Altaras et al. teaches mutant *E. coli*, comprising deletion of its *ldhA* gene and over-expression of gldA and mgs, having increased production of 1,2-propanediol and Bermejo et al. teaches expression of a *C. acetobutylicum* gene encoding an

enzyme that increases production of acetone in *E. coli* in order to decrease accumulation of acetate.

Therefore, the above references render claims 1-6, 9-14, 16, 22-27, 30-36, 39-46, and 48-50 *prima facie* obvious.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants argue that Cameron et al. does not teach "evolving" or "evolved" strains. The rejection has been amended. The phrase “causing evolution” comprises genetic engineering, such as deletion of genes. Therefore, in combining the above references, one having ordinary skill in the art would have recognized the advantage of further “evolving” the microorganism of Cameron et al.

Applicants argue that one of ordinary skill in the art would have no motivation to delete the ldhaA gene alone with an expectation that such a deletion would result in enhanced production of 1,2-propanediol because Altaras et al. teachs that the specific overexpression of certain genes in combination with the deletion of other genes may result in enhanced production of 1,2-propanediol. Examiner respectfully disagrees. The claims do not exclude modifying genes (either via inactivation or up-regulation) that are not recited in the claims. In order to further increase the ethanol yield of the microorganism of Cameron et al., one having ordinary skill in the art would have been motivated to further modify the microorganism of Cameron et al. by adopting the various combinations of gene taught by Altaras et al.

Applicants also argue that there is no motivation as to why one of ordinary skill in the art would simultaneously delete *ldhaA* while at the same time increasing expression of a *C. acetobutylicum* gene. Examienr respectfully disagrees. One of ordinary skill in the art at the time the invention was made would have been motivated to do the above for the purpose of pushing the carbon flux towards 1,2-propanediol by eliminating production of the byproduct, lactate, and decrease accumulation of acetate.

Hence the rejection is maintained.

Conclusion

None of the claims are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Yong D Pak/
Primary Examiner, Art Unit 1652